THE SALK INSTITUTE

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Systems Development Foundation
181 Lytton Avenue
Palo Alto, California

Attached is a request from Dr. F. H. C. Crick at The Salk Institute, for funds to set up and maintain a small group in theoretical neurobiology, together with funds to carry out related experimental work at The Salk Institute.

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Introduction

Ever since the birth of the modern electronic computer, people have made the comparison between computers and the brain. As is well known, there are many differences. Computers are digital. Neurons are more like analogue elements, except for the all-or-none signal down an axon. The "pulse rate" of a modern computer is very fast; that of the brain relatively slow. However the most significant difference is that the brain is a machine using highly parallel processes, while a computer is largely serial. In addition each element in the brain (each neuron) makes hundreds or thousands of connections (synapses) whereas in a computer each element has rather few connections. Moreover these connections in the brain are unlikely to be all-or-none.

Because of these differences, the theories used to describe computers are inadequate to deal with the computations carried out by the brain. A new form of theory is required. Thus the brain is now of considerable interest to those concerned with systems handling large amounts of information, since a detailed knowledge of its operations may suggest radically new ways of building communication systems. For example, the way memory is stored in a modern computer is unlikely to be the way it is handled in the brain.

The earlier theoretical approaches to the brain described models of nerve nets of various kinds. These showed that it was possible to learn and store considerable information in such nets in a way which was distributed, redundant, and overlapping. The nets were very idealized and only faintly resembled real circuits in the brain. Nor was much attention paid as to what exact jobs these nets needed to do.

In the last few years a new approach to the higher nervous system has arisen. This might be described as the "computational approach". A good example would be David Marr's ideas on the visual system (to be published soon in his posthumus book Vision). For the visual system it means considering the broad features of the world we see (that it consists largely of solid objects, each in its place, etc.), some evidence as to how we see it (from psychophysics), and the limitations imposed by communication theory. Marr distinguished three levels of explanation: 1) computational theory, 2) algorithm (i.e., how to do the calculations), and 3) implementation. He was least concerned with the latter: how the neurons are wired together and how they interact.

I intend to pursue a wider approach, consisting of the one just described plus a lot of evidence from neuroanatomy, neurophysiology, evoked potentials, positive emission tomography (PET) and so on, which does concern itself with the detailed wiring and activity inside the brain. This might be called the Integrated Computational Approach. To do this I need frequent contact with experimental groups working in this area.

One immediately runs into a technical limitation. Experiments in psychophysics can be done quickly and cheaply on human subjects. They are much more laborious and expensive for monkeys or other vertebrates. On the other hand, methods of single-cell recording are very difficult to do on man but easily possible on animals. In addition the newer and more powerful methods of neuroanatomy are difficult or impossible to do on man for ethical reasons.

Thus a combined approach, using some data from humans and some from monkeys, cats, etc., is likely to be the best strategy. At the same time it is desirable to develop new experimental methods to overcome some of these limitations, and especially to exploit non-invasive methods for studying man, such as evoked potentials, PET, "squid" magnetic detectors, etc. The hope is that it will be possible to tie together theory, psychophysics, neurophysiology, neuroanatomy and molecular biology in at least a few specially favorable cases. Details of such an approach were given to the Board in my presentation of October 20, 1981.

My own primary interest is in the visual system, mainly because we are very visual animals (contrast smell), because the input is easy to control and because so much good experimental work has already been done on it, but I am also concerned with other cortical functions. Other theorists (for example, Zipser) are especially interested in the oculomotor system, which has the advantage of producing a well-defined output. Other possible candidates are the auditory system and the somatosensory system. The study of human language has an obvious appeal through it has the disadvantage that one lacks a good experimental animal.

All these systems are likely to have some elements and functions in common. A decisive advance in one is likely to assist the study of the others.

This approach does not deal with the entire behavior of higher nervous systems. It is mainly concerned with the detailed processing of highly complex information. It is less concerned with such matters as pain, emotion, mood, appetite, temperature control, etc.

The General Plan

The general plan is to create a small theoretical neurobiology group at The Salk Institute (about three or four scientists in all) under my leadership and to support this with an active visitors program. This group would interact with theorists at UCSD and with experimentalists in the area, especially with those actively working at The Salk Institute. To encourage this collaboration, funds are also requested so that I can support carefully selected experimental projects at The Salk Institute which fall within this program.

Duration

Support is requested for five years. This is partly because it would be very difficult to recruit the more senior people if support were for a lesser period, and partly because I am now 65 years of age: five years support would take me to the retirement age.

The Detailed Proposal

This request for a five year program falls into six parts.

I. Support for myself

This needs little comment, except that I expect to spend 70-90% of my time on this type of work. (I am funded partly from other sources.)

II. Support for two or three colleagues in the theoretical work.

I suggest one senior appointment (perhaps David Zipser), one junior appointment and one graduate student, postgraduate or assistant. It is not simple to make the first two appointments, both because The Salk Institute cannot offer indefinite tenure and because, the group being small, the people must be carefully selected to work well together. At least one of these two should be a professional mathemetician.

III. The visitors program

The advantages of this are obvious. While people may be reluctant to move to La Jolla, they need little tempting to visit Southern California. The visitors program would promote useful interactions between theorists, and between theorists and experimentalists. (Theorists, incidentally, usually find it is easier to get away for a month or two than do experimentalists.)

The suggested program falls under three heads:

i. Seminars. I expect one seminar a month for nine months each year.

ii. Longer visits (2 weeks to 2-3 months). I expect 14 man-months per year. (Such visitors could normally be accommodated in two offices). Realistic allowances have been made for travel, both from the East coast and from Europe.

iii. An annual workshop. I propose that we have one small workshop a year at The Salk Institute (12-15 people for 1-2 weeks). A topic would be chosen which would appear to be timely.

In all the items in this section care has been taken to ask for no more visitors per year than we feel can comfortably be fitted in without disrupting our own work.

IV. The experimental program

The Salk Institute employs about 75 scientists with Ph.D.'s on various aspects of neurobiology with a roughly equal number of auxilliary laboratory staff. The total budget for all this amounts to $10 million per annum. Clearly our proposed program could only be a small fraction of this.

I plan to use three criteria to judge projects in The Salk Institute which might be carried out for this program.

A. It must fall within the general area of the Integrated Computational Approach, though it's relevance may be long-term.

B. It must be of interest to me personally or to one of my close associates.

C. It should usually be for work which it is not easy to fund from other sources.

As a first step I have identified work already planned or even in progress to some extent, which would satisfy these criteria. Such are:

<u>Dr. Max Cowan's group</u>

- experiments to detect actin in dendritic spines (being done at my suggestion) by Dr. Cowan.
- experiments on area 7, one of the later visual areas of the cortex, by Dr. Richard Anderson. The neuroanatomy is

in progress. The apparatus for doing the neurophysiology is being set up.

- experiments to develop new or improved methods of neuroanatomy. Some work in progress by various people.

Dr. Cowan tells me that at the moment these projects are fairly well financed so that only a modest contribution is needed to keep the work going.

Dr. Floyd Bloom's group

- experiments on the distribution of peptides (such as VIP, somatostatin, and cholecystokinin) in the cortex and the characteristics of the neurons containing them, using both the light microscope and the electron microscope.
- the diffuse inervation of the cortex

These studies by Dr. John Morrison and Elena Battenberg are in progress only to a limited extent because they are not adequately financed.

Dr. Helen Neville's group

- work with Dr. Richard Anderson on evoked potentials in the macaque, combined with neurophysiological studies by him.
- collaboration with Dr. Benabid (of Grenoble) who recently spent a year at The Salk Institute. He plans to record evoked potentials from deep in the human brain during exploratory surgery.
- evoked potential study in man (and possibly monkeys) on a whole variety of visual stimuli.

None of these is as yet properly funded, although Dr. Benabid has funds for his part of the collaboration.

It is certain that any scheme of this sort, if handled sensibly, is bound to start slowly and then increase appreciably as new ideas come along. Such funding provides the possibility

of using relatively small sums of money to influence The Salk Institute's research program in neurobiology in a very significant way from my program's point of view.

V. Post-doctoral training

A most valuable use of money would be to provide two Fellowships at The Salk Institute for post-docs (from elsewhere) of very high quality whose work falls within this program. Such people are difficult to tempt here unless money can be promised without delay. Any particular individual would normally only need such money for a year or so (since he is then likely to be funded from other sources), so the Fellowships could be rolled over from one person to another.

I regard this as an excellent way of making a small sum of money do a most useful job which is difficult to fund in other ways. The Fellowships might be called SDF Fellowships.

VI. The psychophysics of vision

I propose that my colleagues and I, and also such visitors who are interested, have a facility for psychophysics experiments on the human visual system. This is a relatively inexpensive form of research which theorists often find very attractive. (I think it a good idea to have theorists do some experiments, if only to keep their feet on the ground.)

Collaboration with UCSD

There are many groups at UCSD with whom we might collaborate in an informal manner, but there is one with which we expect to have a closer relationship. This is the Psychology Department and in particular the group led by Professor Donald Norman.

We would hope, since we are scarcely a mile apart, that our small group would interact with him and his staff, by attending each other's seminars, visiting each other's

labs, having lunch together, etc. However I would propose that there is one matter on which Don Norman and I should consult together on a more formal basis: this is the visitors program, including the annual workshop. I suggest that we form a committee of two to decide whom to invite to La Jolla in this program. Professor Norman tells me he would be happy to collaborate in this way.